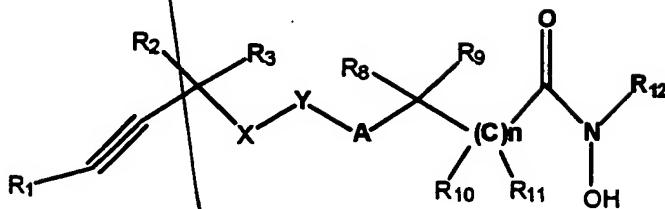


## **CLAIMS**

### **What is claimed:**

## 1. A compound of formula



**wherein:**

10 R<sub>1</sub> is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or C<sub>5</sub>-C<sub>8</sub>-cycloheteroalkyl having from 1-2 heteroatoms selected from N, NR<sub>7</sub>, S and O;

15 R<sub>2</sub> and R<sub>3</sub> are each independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH<sub>3</sub>;

R<sub>5</sub> is hydrogen, alkyl of 1-8 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, or C<sub>4</sub>-C<sub>8</sub>-cycloheteroalkyl;

20 R<sub>7</sub> is hydrogen, aryl, aralkyl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms, oxy, C<sub>1</sub>-C<sub>8</sub> alkanoyl, COOR<sub>5</sub>, COR<sub>5</sub>, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>8</sub> alkyl, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-heteroaryl, -CO-NHR<sub>i</sub>;

25 R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, and R<sub>11</sub> are each, independently, hydrogen, aryl, aralkyl, 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR<sub>7</sub>, O and S, heteroaralkyl having from 1-3 heteroatoms selected from N, NR<sub>7</sub>, O and S, cycloalkyl of 3-6 carbon atoms, -C<sub>4</sub>-C<sub>8</sub>-cycloheteroalkyl having from 1-3 heteroatoms selected from N, NR<sub>7</sub>, O and S, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms;

*BB  
CJ  
5*

R<sub>12</sub> is hydrogen, aryl or 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR<sub>7</sub>, S and O, cycloalkyl of 3-6 carbon atoms, -C<sub>5</sub>-C<sub>8</sub>-cycloheteroalkyl having from 1 to 2 heteroatoms selected from N, NR<sub>7</sub>, S and O, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO<sub>2</sub>, NR<sub>7</sub>, or CH<sub>2</sub>;

X is O, S, SO, SO<sub>2</sub>, NR<sub>7</sub>, or CH<sub>2</sub>;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

10

2. A compound of Claim 1 wherein Y is phenyl, pyridyl, thienyl, furanyl, imidazolyl, triazolyl or thiadiazolyl.
3. A compound of Claim 1 wherein R<sub>1</sub> and R<sub>2</sub> are each, independently, hydrogen or alkyl of 1-6 carbon atoms; R<sub>12</sub> is hydrogen; and Y is phenyl.

15

4. A compound of Claim 1 selected from the group consisting of:  
2-(4-But-2-nyloxy-benzenesulfonyl)-N-hydroxy-2-methyl-3-pyridin-3-yl-propionamide;  
2-(4-But-2-nyloxy-phenylsulfonyl)-N-hydroxy-propionamide;  
2-(4-But-2-nyloxy-benzenesulfonyl)-N-hydroxy-2-methyl-3-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-propionamide;

20

- 3-Biphenyl-4-yl-2-(4-but-2-nyloxy-benzenesulfonyl)-N-hydroxy-2-methyl-propionamide;  
2-(4-But-2-nyloxy-phenylsulfonyl)-octanoic acid hydroxamide;  
2-(But-2-nyloxy-benzenesulfonyl)-octanoic acid hydroxamide;

25

- 2[(R)-(4-Butyl-2-nyloxy)-sulfinyl-N-hydroxyoctanamide;  
2[(S)-(4-Butyl-2-nyloxy)-sulfinyl-N-hydroxyoctanamide;  
3-(4-But-2-nyloxy-phenoxy)-N-hydroxy-propionamide  
4-(4-But-2-nyloxy-phenoxy)-N-hydroxy-butyramide;

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2-(4-But-2-nyloxy-phenoxy)-N-hydroxy-acetamide;  
4-(4-But-2-nyloxy-phenyl)-N-hydroxy-butyramide;  
Quinoline-2-carboxylic acid [5-(4-but-2-nyloxy-phenylsulfanyl)-5-  
hydroxycarbamoyl-pentyl]-amide;

5 2-(4-But-2-nyloxy-phenylsulfanyl)-6-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-  
yl)-acetylamino]-hexanoic acid hydroxyamide;

N-[5-(4-But-2-nyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentyl]-2-  
phenethyl-benzamide;

10 2-(4-But-2-nyloxy-phenylsulfanyl)-6-[2-(3,4-dichloro-phenyl)-acetylamino]-  
hexanoic acid hydroxyamide;

Quinoline-3-carboxylic acid [5-(4-but-2-nyloxy-phenylsulfanyl)-  
5-hydroxycarbamoyl-pentyl]-amide;

2-(4-But-2-nyloxy-phenylsulfanyl)-6-(4-thiophen-2-yl-butyryl amino)-  
hexanoic acid hydroxyamide;

15 9H-Xanthene-9-carboxylic acid [5-(4-but-2-nyloxy-phenylsulfanyl)-  
5-hydroxycarbamoyl-pentyl]-amide;

2-(4-But-2-nyloxy-phenylsulfanyl)-6-diphenylacetyl amino-  
hexanoic acid hydroxyamide;

Isoquinoline-1-carboxylic acid [5-(4-but-2-nyloxy-phenylsulfanyl)-  
20 5-hydroxycarbamoyl-pentyl]-amide;

6-(2-Benzo[b]thiophen-3-yl-acetyl amino)-2-(4-but-2-nyloxy-phenyl-  
sulfanyl)-hexanoic acid hydroxyamide;

Quinoline-2-carboxylic acid [5-(4-but-2-nyloxy-benzenesulfinyl)-  
5-hydroxycarbamoyl-pentyl]-amide;

25 2-(4-But-2-nyloxy-benzenesulfinyl)-6-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-  
yl)-acetylamino]-hexanoic acid hydroxyamide;

N-[5-(4-But-2-nyloxy-benzenesulfinyl)-5-hydroxycarbamoyl-pentyl]-2-  
phenethyl-benzamide;

2-(4-But-2-nyloxy-benzenesulfinyl)-6-[2-(3,4-dichloro-phenyl)-  
acetylamino]-hexanoic acid hydroxyamide;

Quinoline-3-carboxylic acid [5-(4-but-2-nyloxy-benzenesulfinyl)-5-  
hydroxycarbamoyl-pentyl]-amide;

5 2-(4-But-2-nyloxy-benzenesulfinyl)-6-(4-thiophen-2-yl-butyrylamino)-  
hexanoic acid hydroxyamide;

9H-Xanthene-9-carboxylic acid [5-(4-but-2-nyloxy-benzenesulfinyl)-  
5-hydroxycarbamoyl-pentyl]-amide;

2-(4-But-2-nyloxy-benzenesulfinyl)-6-diphenylacetylamino-hexanoic  
10 acid hydroxyamide;

Isoquinoline-1-carboxylic acid [5-(4-but-2-nyloxy-benzenesulfinyl)-  
5-hydroxycarbamoyl-pentyl]-amide;

6-(2-Benzo[b]thiophen-3-yl-acetylamino)-2-(4-but-2-nyloxy-benzene-  
sulfinyl)-hexanoic acid hydroxyamide;

15 2-(4-But-2-nyloxy-benzenesulfinyl)-6-(2-1H-indol-3-yl-acetylamino)-  
hexanoic acid hydroxyamide;

Quinoline-2-carboxylic acid [5-(4-but-2-nyloxy-benzenesulfonyl)-5-  
hydroxycarbamoyl-pentyl]-amide;

2-(4-But-2-nyloxy-benzenesulfonyl)-6-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-  
yl)-acetylamino]-hexanoic acid hydroxyamide;

20 N-[5-(4-But-2-nyloxy-benzenesulfonyl)-5-hydroxycarbamoyl-pentyl]-2-  
phenethyl-benzamide;

2-(4-But-2-nyloxy-benzenesulfonyl)-6-[2-(3,4-dichloro-phenyl)-acetyl-  
amino]-hexanoic acid hydroxyamide;

25 Quinoline-3-carboxylic acid [5-(4-but-2-nyloxy-benzenesulfonyl)-5-  
hydroxycarbamoyl-pentyl]-amide;

9H-Xanthene-9-carboxylic acid [5-(4-but-2-nyloxy-benzenesulfonyl)-  
5-hydroxycarbamoyl-pentyl]-amide;

2-(4-But-2-nyloxy-benzenesulfonyl)-6-diphenylacetylaminohexanoic acid hydroxyamide;  
Isoquinoline-1-carboxylic acid [5-(4-but-2-nyloxy-benzenesulfonyl)-5-hydroxycarbamoyl-pentyl]-amide;  
5  
6-(2-Benzo[b]thiophen-3-yl-acetylamino)-2-(4-but-2-nyloxy-benzene-sulfonyl)-hexanoic acid hydroxyamide;  
Quinoline-2-carboxylic acid {[5-(4-but-2-nyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;  
2-(4-But-2-nyloxy-phenylsulfanyl)-6-{2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetylamino]-acetylamino}hexanoic acid hydroxyamide;  
10  
N-{{[5-(4-But-2-nyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-2-phenethyl-benzamide;  
2-(4-But-2-nyloxy-phenylsulfanyl)-6-{2-[2-(3,4-dichloro-phenyl)-acetylamino]-acetylamino}hexanoic acid hydroxyamide;  
15  
Quinoline-3-carboxylic acid {[5-(4-but-2-nyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;  
9H-Xanthene-9-carboxylic acid {[5-(4-but-2-nyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;  
2-(4-But-2-nyloxy-phenylsulfanyl)-6-(2-diphenylacetylamino-acetylamino)-hexanoic acid hydroxyamide;  
20  
Isoquinoline-1-carboxylic acid {[5-(4-but-2-nyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;  
1-Methyl-1H-pyrrole-2-carboxylic acid {[5-(4-but-2-nyloxy-phenylsulfanyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;  
25  
6-[2-(2-Benzo[b]thiophen-3-yl-acetylamino)-acetylamino]-2-(4-but-2-nyloxy-phenylsulfanyl) hexanoic acid hydroxyamide;  
Quinoline-2-carboxylic acid {[5-(4-but-2-nyloxy-benzenesulfinyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;

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2-(4-But-2-nyloxy-benzenesulfinyl)-6-{2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetyl amino]-acetyl amino}-hexanoic acid hydroxyamide;  
N-{{5-(4-But-2-nyloxy-benzenesulfinyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-2-phenethyl-benzamide;

5 2-(4-But-2-nyloxy-benzenesulfinyl)-6-{2-[2-(3,4-dichloro-phenyl)-acetyl amino]-acetyl amino}-hexanoic acid hydroxyamide;  
Quinoline-3-carboxylic acid {[5-(4-but-2-nyloxy-benzenesulfinyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}amide;  
2-(4-But-2-nyloxy-benzenesulfinyl)-6-[2-(4-thiophen-2-ylbutyryl amino)-acetyl amino]-hexanoic acid hydroxyamide;

10 9H-Xanthene-9-carboxylic acid {[5-(4-but-2-nyloxy-benzenesulfinyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;  
2-(4-But-2-nyloxy-benzenesulfinyl)-6-(2-diphenylacetyl amino-acetyl amino)-hexanoic acid hydroxyamide;

15 1-Methyl-1H-pyrrole-2-carboxylic acid {[5-(4-but-2-nyloxy-benzene-sulfinyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide ;  
2-(4-But-2-nyloxy-benzenesulfonyl)-6-{2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetyl amino]-acetyl amino}-hexanoic acid hydroxyamide;  
N-{{5-(4-But-2-nyloxy-benzenesulfonyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-2-phenethyl-benzamide;

20 2-(4-But-2-nyloxy-benzenesulfonyl)-6-{2-[2-(3,4-dichloro-phenyl)-acetyl amino]-acetyl amino}-hexanoic acid hydroxyamide;  
Quinoline-3-carboxylic acid {[5-(4-but-2-nyloxy-benzenesulfonyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}amide;  
9H-Xanthene-9-carboxylic acid {[5-(4-but-2-nyloxy-benzenesulfonyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;

25 2-(4-But-2-nyloxy-benzenesulfonyl)-6-(2-diphenylacetyl amino-acetyl amino)-hexanoic acid hydroxyamide;

Isoquinoline-1-carboxylic acid {[5-(4-but-2-nyloxy-benzenesulfonyl)-5-hydroxycarbamoyl-pentylcarbamoyl]-methyl}-amide;  
6-[2-(2-Benzo[b]thiophen-3-yl)-acetylamino]-acetylamino]-2-(4-but-2-nyloxy benzenesulfonyl hexanoic acid hydroxyamide;  
5 2-(4-But-2-nyloxy-benzenesulfonyl)-6-[2-(2-1H-indol-3-yl-acetylamino)-acetylamino]-hexanoic acid hydroxyamide;  
2-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-4-{4-[2-(1-piperidinyl)ethoxy phenyl]butanamide;  
2-{[4-(2-butynyloxy)phenyl]sulfonyl}-7-cyano-N-hydroxy heptanamide;  
10 2-{[4-(2-butynyloxy)phenyl]sulfanyl}-2-cyclohexyl-N-hydroxyacetamide;  
2-{[4-(2-butynyloxy)phenyl]sulfinyl}-2-cyclohexyl-N-hydroxyacetamide;  
2-{[4-(2-butynyloxy)phenyl]sulfonyl}-2-cyclohexyl-N-hydroxyacetamide;  
2-{[4-(2-butynyloxy)phenyl]sulfanyl}-N-hydroxy-2-(4-methoxyphenyl)acetamide;  
15 (2R)-2-{[4-(2-butynyloxy)phenyl] sulfanyl}-N-hydroxy-2-(4-methoxyphenyl)ethanamide;  
(2S)-2-{[4-(2-butynyloxy)phenyl] sulfanyl}-N-hydroxy-2-(4-methoxyphenyl)ethanamide;  
2-{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-(4-methoxyphenyl)acetamide;  
20 2-{[4-(2-butynyloxy)phenyl]sulfanyl}-2-(4-chlorophenyl)-N-hydroxyacetamide;  
2-{[4-(2-butynyloxy)phenyl]sulfinyl}-2-(4-chlorophenyl) N-hydroxyacetamide;  
2-{[4-(2-butynyloxy)phenyl]sulfonyl-2-(4-chlorophenyl)-N-hydroxy-acetamide;  
2-{[4-(2-butynyloxy)phenyl]sulfanyl}-2-(3-chlorophenyl)-N-hydroxyacetamide;  
25 2-{[4-(2-butynyloxy)phenyl]sulfonyl}-2-(3-chlorophenyl)-N-hydroxyacetamide;  
2-(4-bromophenyl)-2-{[4-(2-butynyloxy)phenyl]sulfanyl-N-hydroxyacetamide;  
(2S)-2-(4-bromophenyl)-2-{[4-(2-butynyloxy)phenyl]sulfinyl-N-hydroxy-acetamide;

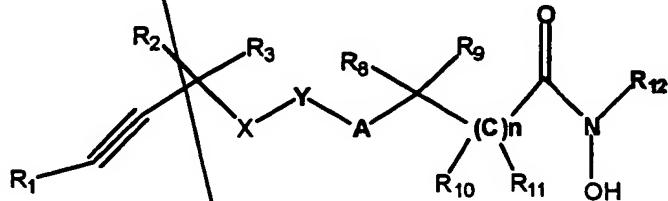
(2R)-2-(4-bromophenyl)-2-{{[4-(2-butynyloxy)phenyl] sulfinyl-N-hydroxy-  
acetamide;  
2-(4-bromophenyl)-2-{{[4-(2-butynyloxy)phenyl]sulfonyl-N-hydroxy-acetamide;  
2{{[4-(2-butynyloxy)phenyl]sulfanyl}-N-hydroxy-2-[4-(2-thienyl)phenyl]-  
acetamide;  
5 (2R)-2-{{[4-(2-butynyloxy)phenyl] sulfinyl}- N-hydroxy-2-[4-(2-thienyl)-  
phenyl]ethanamide;  
2-{{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-[4-(2-thienyl)-  
phenyl]acetamide;  
10 2-{{[4-(2-Butynyloxy)phenyl]sulfanyl}-N-hydroxy-2-(1-naphthyl)acetamide;  
2-{{[4-(2-Butynyloxy)phenyl]sulfinyl}-N-hydroxy-2-(1-naphthyl)acetamide;  
2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-(1-naphthyl)acetamide;  
2-{{[4-(2-Butynyloxy)phenyl]sulfanyl}-2-(4-fluorophenyl)-N-hydroxy-2-(1-  
naphthyl)acetamide;  
15 2-{{[4-(2-butynyloxy)phenyl]sulfinyl-2-(4-fluorophenyl)-N-hydroxyacetamide;  
2-{{[4-(2-butynyloxy)phenyl]sulfanyl-2-(4-fluorophenyl)-N-hydroxyacetamide;  
2-(2-methoxyphenyl)-2-{{[4-(2-butynyloxy)phenyl]sulfanyl-N-hydroxy-  
acetamide;  
2-(2-methoxyphenyl)-2-{{[4-(2-butynyloxy)phenyl]sulfinyl}-N-hydroxy-  
acetamide;  
20 2-{{[4-(2-butynyloxy)phenyl]sulfanyl-N-hydroxy-2-(4-ethoxyphenyl) acetamide;  
2-{{[4-(2-Butynyloxy)phenyl] sulfinyl-N-hydroxy-2-(4-ethoxyphenyl)  
acetamide;  
2-{{[4-(2-butynyloxy)phenyl]sulfonyl-2-(4-chlorophenyl)-N-hydroxyacetamide;  
25 2-{{[4-(2-Butynyloxy)phenyl]sulfanyl-N-hydroxy-2-(3-bromophenyl)  
acetamide;  
(2R)-2-{{[4-(2-butynyloxy)phenyl]sulfinyl-N-hydroxy-2-(3-bromophenyl)  
acetamide;

(2S)-2-{{[4-(2-butynyloxy)phenyl] sulfinyl}-N-hydroxy-2-(3-bromophenyl) acetamide;  
2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}-2-(3-bromophenyl)-N-hydroxyacetamide;  
5 2-{{[4-(2-Butynyloxy)phenyl]sulfanyl}-2-isopropyl-N-hydroxyacetamide;  
R-2-{{[4-(2-butynyloxy)phenyl]sulfinyl}-2-isopropyl-N-hydroxyacetamide;  
S-2-{{[4-(2-butynyloxy)phenyl]sulfinyl}-2-isopropyl-N-hydroxyacetamide;  
2-{{[4-(2-butynyloxy)phenyl]sulfonyl}-2-isopropyl-N-hydroxyacetamide;  
2-{{[4-(2-Butynyloxy)phenyl]sulfanyl}-2-phenyl-N-hydroxyacetamide;  
10 R-2-{{[4-(2-butynyloxy)phenyl]sulfinyl}-2-phenyl-N-hydroxyacetamide;  
S-2-{{[4-(2-butynyloxy)phenyl]sulfinyl}-2-phenyl-N-hydroxyacetamide;  
2-{{[4-(2-Butynyloxy)phenyl]sulfanyl}-2-(2-naphthyl)-N-hydroxyacetamide;  
2-{{[4-(2-butynyloxy)phenyl]sulfonyl}-2-(2-naphthyl)-N-hydroxyacetamide;  
2-{{[4-(2-butynyloxy)phenyl]sulfonyl}-2-(2-naphthyl)-N-hydroxyacetamide;  
15 Tert-butyl-4-[1-{{[4-(2-butynyloxy)phenyl]sulfonyl}-2-(hydroxyamino)-2-oxoethyl]-1-piperidine carboxylate;  
2-{{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-(4-piperidinyl) acetamide;  
2-{{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-[1-(4-methoxybenzyl)-4-piperidinyl] acetamide;  
20 2-(1-benzoyl-4-piperidinyl)-2-{{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxyacetamide;  
2-(1-acetyl-4-piperidinyl)-2-{{[4-(2-butynyloxy)phenyl]sulfonyl}-N-hydroxyacetamide;  
2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-tetrahydro-2H-pyran-4yl-acetamide;  
25 2-{{[4-(2-Butynyloxy)phenyl]sulfonyl}-N-hydroxy-2-tetrahydro-2H-thiopyran-4yl-acetamide;

2-{{4-(2-Butynyloxy)phenyl}sulfonyl}-N-hydroxy-2-(1-oxidotetrahydro-2H-thiopyran-4yl) acetamide; and  
2-{{4-(2-Butynyloxy)phenyl}sulfonyl}-N-hydroxy-2-(1,1-dioxidotetrahydro-2H-thiopyran-4yl) acetamide.

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10

5. A method of inhibiting pathological changes mediated by TNF- $\alpha$  converting enzyme (TACE) in a mammal in need thereof which comprises administering to said mammal a therapeutically effective amount of a compound having the formula:



wherein:

R<sub>1</sub> is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or C<sub>5</sub>-C<sub>8</sub>-cycloheteroalkyl having from 1-2 heteroatoms selected from N, NR<sub>7</sub>, S and O;

15 R<sub>2</sub> and R<sub>3</sub> are each independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH<sub>3</sub>;

R<sub>5</sub> is hydrogen, alkyl of 1-8 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, 20 heteroaryl, or C<sub>4</sub>-C<sub>8</sub>-cycloheteralkyl;

R<sub>7</sub> is hydrogen, aryl, aralkyl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms, oxy, C<sub>1</sub>-C<sub>8</sub> alkanoyl, COOR<sub>5</sub>, COR<sub>5</sub>, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>8</sub> alkyl, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-heteroaryl, -CO-NHR<sub>1</sub>;

25 R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, and R<sub>11</sub> are each, independently, hydrogen, aryl, aralkyl, 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR<sub>7</sub>, O

and S, heteroaralkyl having from 1-3 heteroatoms selected from N, NR7, O and S, cycloalkyl of 3-6 carbon atoms, -C4-C8-cycloheteroalkyl having from 1-3 heteroatoms selected from N, NR7, O and S, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms;

5 R<sub>12</sub> is hydrogen, aryl or 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR7, S and O, cycloalkyl of 3-6 carbon atoms, -C5-C8-cycloheteroalkyl having from 1 to 2 heteroatoms selected from N, NR7, S and O, or alkyl of 1-6 carbon atoms;

A is O, S, SO, SO<sub>2</sub>, NR<sub>7</sub>, or CH<sub>2</sub>;

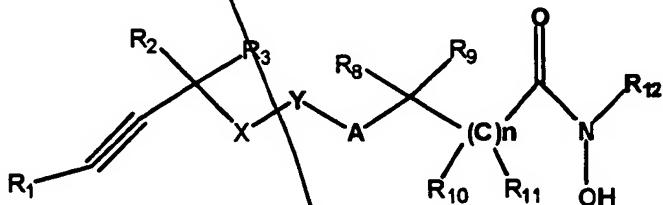
10 X is O, S, SO, SO<sub>2</sub>, NR<sub>7</sub>, or CH<sub>2</sub>;

Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and

n is 0-2; or a pharmaceutically acceptable salt thereof.

15 6. The method of Claim 5 wherein the condition treated is rheumatoid arthritis, graft rejection, cachexia, inflammation, fever, insulin resistance, septic shock, congestive heart failure, inflammatory disease of the central nervous system, inflammatory bowel disease or HIV infection.

7. A pharmaceutical composition comprising a compound having the formula:



25 wherein:

*B3* 5      R<sub>1</sub> is hydrogen, aryl, heteroaryl, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-6 carbon atoms, or C<sub>5</sub>-C<sub>8</sub>-cycloheteroalkyl having from 1-2 heteroatoms selected from N, NR<sub>7</sub>, S and O;

10      R<sub>2</sub> and R<sub>3</sub> are each independently, hydrogen, alkyl of 1-6 carbon atoms, -CN, or -CCH;

      R<sub>5</sub> is hydrogen, alkyl of 1-8 carbon atoms, cycloalkyl of 3-6 carbon atoms, aryl, heteroaryl, or C<sub>4</sub>-C<sub>8</sub>-cycloheteroalkyl;

      R<sub>7</sub> is hydrogen, aryl, aralkyl, alkyl of 1-6 carbon atoms, or cycloalkyl of 3-6 carbon atoms, oxy, C<sub>1</sub>-C<sub>8</sub> alkanoyl, COOR<sub>5</sub>, COR<sub>5</sub>, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>8</sub> alkyl, -SO<sub>2</sub>-aryl, -SO<sub>2</sub>-heteroaryl, -CO-NHR<sub>1</sub>;

15      R<sub>8</sub>, R<sub>9</sub>, R<sub>10</sub>, and R<sub>11</sub> are each, independently, hydrogen, aryl, aralkyl, 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR<sub>7</sub>, O and S, heteroaralkyl having from 1-3 heteroatoms selected from N, NR<sub>7</sub>, O and S, cycloalkyl of 3-6 carbon atoms, -C<sub>4</sub>-C<sub>8</sub>-cycloheteroalkyl having from 1-3 heteroatoms selected from N, NR<sub>7</sub>, O and S, alkyl of 1-18 carbon atoms, alkenyl of 2-18 carbon atoms, alkynyl of 2-18 carbon atoms;

      R<sub>12</sub> is hydrogen, aryl or 5-10 membered heteroaryl having from 1-3 heteroatoms selected from N, NR<sub>7</sub>, S and O, cycloalkyl of 3-6 carbon atoms, -C<sub>5</sub>-C<sub>8</sub>-cycloheteroalkyl having from 1 to 2 heteroatoms selected from N, NR<sub>7</sub>, S and O, or alkyl of 1-6 carbon atoms;

      A is O, S, SO, SO<sub>2</sub>, NR<sub>7</sub>, or CH<sub>2</sub>;

      X is O, S, SO, SO<sub>2</sub>, NR<sub>7</sub>, or CH<sub>2</sub>;

      Y is aryl or heteroaryl, with the proviso that A and X are not bonded to adjacent atoms of Y; and

25      n is 0-2; or a pharmaceutically acceptable salt thereof.